

PRELIMINARY AMENDMENT

Serial Number: Unknown

Filing Date: Herewith

Title: PREVENTION AND TREATMENT OF CARDIOVASCULAR PATHOLOGIES

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D.I.: 295.009US3

68. (Amended) The method of claim [21, 61, 62 or] 63 wherein the compound of formula (I) is toremifene or a pharmaceutically acceptable salt thereof.

69. (Amended) The method of claim [61, 62 or] 63 wherein the administration is to a human patient.

70. (Amended) The method of claim [61, 62 or] 63 wherein the administration is before, during or after said procedure.

71. (Amended) The method of claim [61, 62 or] 63 wherein the administration is in a series of spaced doses.

72. (Amended) The method of claim [61, 62 or] 63 wherein the administration is parenteral.

73. (Amended) The method of claim [61, 62 or] 63 wherein the administration is oral.

74. (Amended) The method of claim [61, 62 or] 63 wherein the administration is systemic.

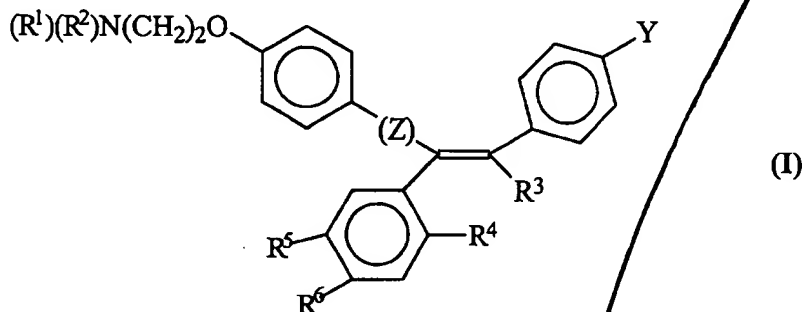
75. (Amended) The method of claim [61, 62 or] 63 wherein the compound of formula (I) is administered via a sustained release dosage form.

76. (Amended) The method of claim [61, 62 or] 63 wherein the administration is localized at the site of the vascular trauma.

77. (Amended) The method of claim [61, 62 or] 63 wherein the compound directly or indirectly increases the level of active TGF-beta.

80. (Amended) A therapeutic method for preventing or treating a cardiovascular or vascular indication characterized by a decreased lumen diameter comprising administering to a mammal at risk of or afflicted with said cardiovascular or vascular indication, a cytostatic

dose of a therapeutic agent, wherein the therapeutic agent is a compound of formula (I):



wherein Z is C=O or a covalent bond; Y is H or O(C<sub>1</sub>-C<sub>4</sub>)alkyl, R<sup>1</sup> and R<sup>2</sup> are individually (C<sub>1</sub>-C<sub>4</sub>)alkyl or together with N are a saturated heterocyclic group, R<sup>3</sup> is ethyl or chloroethyl, R<sup>4</sup> is H, R<sup>5</sup> is I, O(C<sub>1</sub>-C<sub>4</sub>)alkyl or H and R<sup>6</sup> is I, O(C<sub>1</sub>-C<sub>4</sub>)alkyl or H with the proviso that when R<sup>4</sup>, R<sup>5</sup>, and R<sup>6</sup> are H, R<sup>3</sup> is not ethyl; or a pharmaceutically acceptable salt thereof.

81. (Amended) The method of claim 80 wherein the cytostatic dose is effective to increase the level of TGF-beta so as to [decrease lesion formation or development,] inhibit smooth muscle cell proliferation, inhibit lipid accumulation, increase plaque stability, maintain or increase vessel lumen diameter, or any combination thereof.

95. (Amended) The method of claim 89 [or 90] wherein the increase in TGF-beta reduces or inhibits diabetic retinopathy.

99. (Amended) The method of claim [1, 2, 21 or] 89 wherein the compound is a TGF-beta production stimulator.

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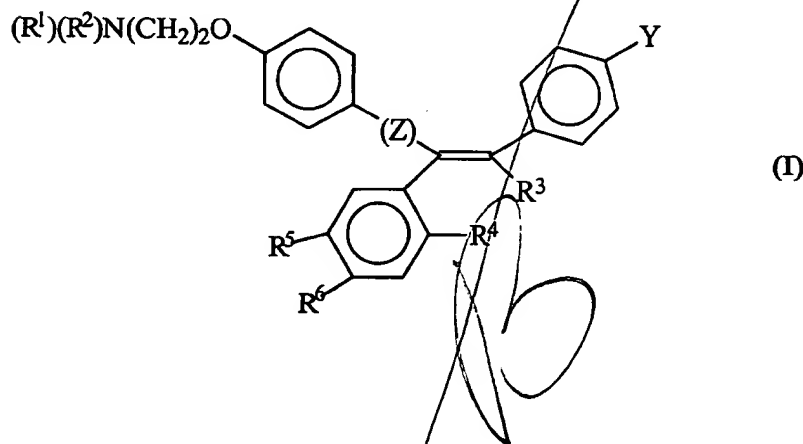
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100. (Amended) The method of claim [1, 2, 21 or] 89 wherein the compound is a TGF-beta activator.
101. (Amended) The method of claim [1, 2, 21 or] 89 wherein the compound increases the production of TGF-beta mRNA.
102. (Amended) The method of claim [1, 2, 21 or] 89 wherein the compound increases the cleavage of the latent form of TGF-beta.
103. (Amended) The method of claim [1, 2, 21 or] 89 wherein the compound increases the bioavailability of TGF-beta.
108. (Amended) The method of claim [1, 2, 21, 61, 62,] 63 [, 80 or] 89 wherein the compound forms cellular DNA adducts at level which is reduced relative to DNA adduct formation by tamoxifen.
109. (Amended) The method of claim [1, 2, 21, 61, 62,] 63 [, 80 or] 89 wherein the compound has estrogenic activity which is reduced relative to the estrogenic activity of tamoxifen.
110. (Amended) The method of claim [21, 61, 62, 63 [, 80 or] 89 wherein the compound does not form cellular DNA adducts.
111. (Amended) The method of claim [1, 2, 21, 61, 62, 63 [, 80 or] 89 wherein the compound has no estrogenic activity.
118. (Amended) The method of claim [1, 2, 21, 61, 62,] 63, [80,] 89[, 90] or 112 wherein the administration increases the level of latent TGF-beta relative to the level of latent TGF-beta prior to said administration.

119. (Amended) The method of claim [1, 2, 21, 61, 62,] 63, [80,] 89[, 90] or 112 wherein the administration increases the level of active TGF-beta relative to the level of active TGF-beta prior to said administration.
120. (Amended) A therapeutic method for preventing or treating a [cardiovascular or] vascular indication characterized by a decreased lumen diameter comprising administering to a mammal at risk of or afflicted with said [cardiovascular or] vascular indication, a cytostatic dose of a therapeutic agent, wherein the therapeutic agent is a compound of formula (I):



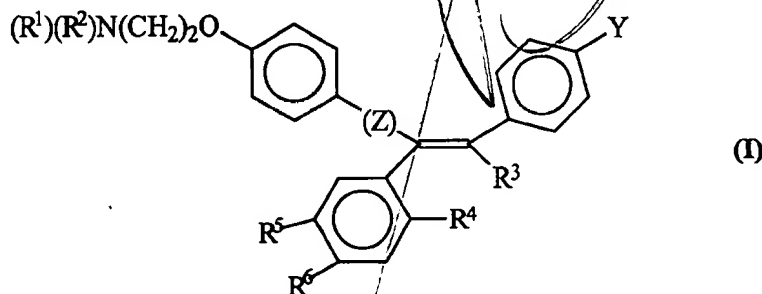
wherein Z is C=O or a covalent bond; Y is H or O(C<sub>1</sub>-C<sub>4</sub>)alkyl, R<sup>1</sup> and R<sup>2</sup> are individually (C<sub>1</sub>-C<sub>4</sub>)alkyl or together with N are a saturated heterocyclic group, R<sup>3</sup> is ethyl or chloroethyl, R<sup>4</sup> is H or together with R<sup>3</sup> is -CH<sub>2</sub>-CH<sub>2</sub>- or -S-, R<sup>5</sup> is I, OH, O(C<sub>1</sub>-C<sub>4</sub>)alkyl or H and R<sup>6</sup> is I, O(C<sub>1</sub>-C<sub>4</sub>)alkyl or H with the proviso that when R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> are H, R<sup>3</sup> is not ethyl; or a pharmaceutically acceptable salt thereof.

135. (Amended) The intravascular stent of [any one of claims 122 to 129] claim 129 wherein the compound of formula (I) is in a sustained release dosage form.

- AS 136. (Amended) The intravascular stent of [any one of claims 122 to 129] claim 129 wherein the matrix of the stent comprises the compound of formula (I).

Please add the following new claims:

153. (New) The method of claim 120 wherein the compound of formula (I) is idoxifene, 4-iodotamoxifen, 3-iodotamoxifen, toremifene, or a pharmaceutically acceptable salt thereof.
154. (New) The method of claim 120 wherein the administration is systemic.
155. (New) The method of claim 120 wherein the compound of formula (I) is administered in a sustained release dosage form.
156. (New) A therapeutic method for treating a condition selected from the group consisting of arteriosclerosis and small vessel disease, comprising administering to a mammal afflicted with said condition, an effective amount of a compound of formula (I):



wherein Z is C=O or a covalent bond; Y is H or O(C<sub>1</sub>-C<sub>4</sub>)alkyl, R<sup>1</sup> and R<sup>2</sup> are individually (C<sub>1</sub>-C<sub>4</sub>)alkyl or together with N are a saturated heterocyclic group, R<sup>3</sup> is ethyl or